CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074649

Trade Name : CARBAMAZEPINE TABLETS 200MG

Generic Name: Carbamazepine Tablets 200mg

Sponsor :Taro Pharmaceuticals, U.S.A., Inc.

Approval Date: October 3, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074649

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074649

APPROVAL LETTER

ANDA 74-649

OCT 3 1996

Taro Pharmaceuticals U.S.A., Inc.
Agent for: Taro Pharmaceuticals Industries LTD.
Attention: Timothy A. Anderson, M.S., M.B.A.
6 Skyline Drive
Hawthorne, NY 10532

Dear Sir:

This is in reference to your abbreviated new drug application dated March 17, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Carbamazepine Tablets USP, 200 mg.

Reference is also made to your amendments dated October 16, 1995, and August 20 and September 6, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Carbamazepine Tablets USP, 200 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Tegretol® Tablets, 200 mg of Ciba Geigy Corporation. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

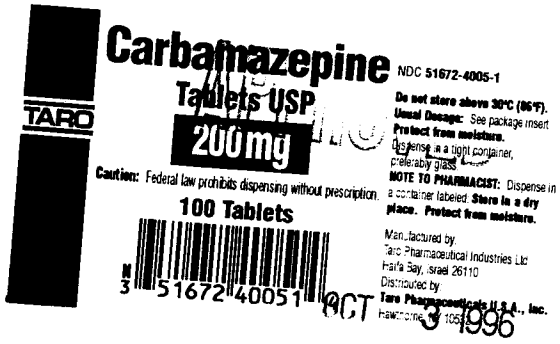
/S/ 10/3/96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074649

FINAL PRINTED LABELING


TARO
Carbamazepine
Tablets USP
200 mg
Caution: Federal law prohibits dispensing without prescription.
100 Tablets
NDC 51672-4005-1
Do not store above 30°C (86°F).
Usual Dosage: See package insert
Protect from moisture.
Dispense in a tight container, preferably glass.
NOTE TO PHARMACIST: Dispense in a container labeled Store in a dry place. Protect from moisture.
Manufactured by:
Taro Pharmaceutical Industries Ltd
Haifa Bay, Israel 26110
Distributed by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532
OCT 3 1996

Carbamazepine Tablets USP, 200 mg

Prescribing Information

WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

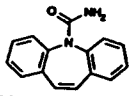
BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON CARBAMAZEPINE ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing carbamazepine, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Carbamazepine USP is an anticonvulsant and specific analgesic for trigeminal neuralgia. Its chemical name is 5*H*-Dibenz[*b,f*]azepine-5-carboxamide, and its structural formula is:

Per USP 23 Monograph



$C_{15}H_{12}N_2O$

Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Each tablet, for oral administration, contains 200 mg carbamazepine. In addition, each tablet contains the following inactive ingredients: Ammonio methacrylate copolymer, diethyl phthalate, microcrystalline cellulose, corn starch, croscarmellose sodium, magnesium stearate.

CLINICAL PHARMACOLOGY

In controlled clinical trials, carbamazepine has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

Mechanism of Action

Carbamazepine has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Carbamazepine greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and lumbar and polysynaptic reflexes, including the flexor monosynaptic reflex in cats. Carbamazepine is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

The principal metabolite of carbamazepine, carbamazepine-10, 11-epoxide, has anticonvulsant activity as demonstrated in several *in vivo* animal models of seizures. Though clinical activity for the epoxide has been postulated, the significance of its activity with respect to the safety and efficacy of carbamazepine has not been established.

Pharmacokinetics

In clinical studies, carbamazepine suspension, conventional tablets, and carbamazepine extended-release tablets delivered equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat faster, and the carbamazepine extended-release tablet slightly slower, than the conventional tablet. The bioavailability of the carbamazepine extended-release tablet was 88% compared to suspension. Following a b.i.d. dosage regimen, the suspension provides higher peak levels and lower trough levels than those obtained from the conventional tablet for the same dosage regimen. On the other hand, following a t.i.d. dosage regimen, carbamazepine suspension affords steady-state plasma levels comparable to carbamazepine tablets given b.i.d. when administered at the same total mg daily dose. Following a b.i.d. dosage regimen, carbamazepine extended-release tablets afford steady-state plasma levels comparable to conventional carbamazepine tablets given q.i.d., when administered at the same total mg daily dose. Carbamazepine in blood is 76% bound to plasma proteins. Plasma levels of carbamazepine are variable and may range from 0.5-25 mcg/mL, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 mcg/mL. In polytherapy, the concentration of carbamazepine and concomitant drugs may be increased or decreased during therapy, and drug effects may be altered (see PRECAUTIONS, Drug Interactions). Following chronic oral administration of suspension, plasma levels peak at approximately 1.5 hours compared to 4-5 hours after administration of conventional carbamazepine tablets, and 3-12 hours after administration of carbamazepine-extended-release tablets. The CSF/serum ratio is 0.22, similar to the 24% unbound carbamazepine in serum. Because carbamazepine induces its own metabolism, the half-life is also variable. Autoinduction is completed after 3-5 weeks of a fixed dosing regimen. Initial half-life values range from 25-65 hours, decreasing to 12-17 hours on repeated doses. Carbamazepine is metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide from carbamazepine. After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged carbamazepine.

The pharmacokinetic parameters of carbamazepine disposition are similar in children and in adults. However, there is a poor correlation between plasma concentrations of carbamazepine and carbamazepine dose in children. Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide (a metabolite shown to be equipotent to carbamazepine as an anticonvulsant in animal screens) in the younger age groups than in adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age (in one report from 0.44 in children below the age of 1 year to 0.18 in children between 10-15 years of age).

The effects of race and gender on carbamazepine pharmacokinetics have not been systematically evaluated.

INDICATIONS AND USAGE

Epilepsy: Carbamazepine tablets are indicated for use as an anticonvulsant drug. Evidence supporting efficacy of carbamazepine as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above or other partial or generalized seizures.

Absence seizures (petit mal) do not appear to be controlled by carbamazepine (see PRECAUTIONS, General).

Trigeminal Neuralgia: Carbamazepine tablets are indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia.

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

Carbamazepine should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of carbamazepine, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome have been reported with carbamazepine. These reactions have been extremely rare. However, a few fatalities have been recorded.

Carbamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

PRECAUTIONS

General: Before initiating therapy, a detailed history and physical examination should be made.

Carbamazepine should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients carbamazepine has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematologic reaction to other drugs, or interrupted courses of therapy with carbamazepine.

Since a given dose of carbamazepine suspension will produce higher peak levels than the same dose given as the tablet, it is recommended that patients given the suspension be started on lower doses and increased slowly to avoid unwanted side effects (see DOSAGE AND ADMINISTRATION).

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Laboratory Tests: Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence or significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy and tonometry are recommended, since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with carbamazepine administered alone.

Hyponatremia has been reported in association with carbamazepine use, either alone or in combination with other drugs.

Interference with some pregnancy tests has been reported.

Drug Interactions: Clinically meaningful drug interactions have occurred with concomitant medications and include, but are not limited to, the following:

Agents That May Affect Carbamazepine Plasma Levels

CYP 3A4 inhibitors inhibit carbamazepine metabolism and can thus increase plasma carbamazepine levels. Drugs that have been shown, or would be expected, to increase plasma carbamazepine levels include:

cimetidine, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clarithromycin, fluoxetine, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, ketoconazole, itraconazole, verapamil, valproate.*

given b.i.d. when administered at the same total daily dose. Carbamazepine attains steady state plasma levels comparable to conventional carbamazepine tablets given q.i.d., when administered at the same total daily dose. Carbamazepine is 70% bound to plasma proteins. Plasma levels of carbamazepine are variable and may range from 0.5-25 mcg/mL, with an apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 mcg/mL. In polytherapy, the concentration of carbamazepine and concomitant drugs may be increased or decreased during therapy, and drug effects may be altered (see PRECAUTIONS, Drug Interactions). Following chronic oral administration of suspension, plasma levels peak at approximately 1.5 hours compared to 4-5 hours after administration of conventional carbamazepine tablets, and 3-12 hours after administration of carbamazepine-extended-release tablets. The CSF/serum ratio is 0.22, similar to the 24% unbound carbamazepine in serum. Because carbamazepine induces its own metabolism, the half-life is also variable. Autoinduction is completed after 3-5 weeks of a fixed dosing regimen. Initial half-life values range from 25-65 hours, decreasing to 12-17 hours on repeated doses. Carbamazepine is metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide from carbamazepine. After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged carbamazepine.

The pharmacokinetic parameters of carbamazepine disposition are similar in children and in adults. However, there is a poor correlation between plasma concentrations of carbamazepine and carbamazepine dose in children. Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide (a metabolite shown to be equipotent to carbamazepine as an anticonvulsant in animal screens) in the younger age groups than in adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age (in one report from 0.44 in children below the age of 1 year to 0.18 in children between 10-15 years of age).

The effects of race and gender on carbamazepine pharmacokinetics have not been systematically evaluated.

INDICATIONS AND USAGE

Epilepsy: Carbamazepine tablets are indicated for use as an anticonvulsant drug. Evidence supporting efficacy of carbamazepine as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above or other partial or generalized seizures.

Absence seizures (petit mal) do not appear to be controlled by carbamazepine (see PRECAUTIONS, General).

Trigeminal Neuralgia: Carbamazepine tablets are indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia.

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

Carbamazepine should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of carbamazepine, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome have been reported with carbamazepine. These reactions have been extremely rare. However, a few fatalities have been reported.

Carbamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

PRECAUTIONS

General: Before initiating therapy, a detailed history and physical examination should be made.

Carbamazepine should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients carbamazepine has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematologic reaction to other drugs, or interrupted courses of therapy with carbamazepine.

Since a given dose of carbamazepine suspension will produce higher peak levels than the same dose given as the tablet, it is recommended that patients given the suspension be started on lower doses and increased slowly to avoid unwanted side effects (see DOSAGE AND ADMINISTRATION).

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Laboratory Tests: Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy and tonometry are recommended, since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with carbamazepine administered alone.

Hyponatremia has been reported in association with carbamazepine use, either alone or in combination with other drugs.

Interference with some pregnancy tests has been reported.

Drug Interactions: Clinically meaningful drug interactions have occurred with concomitant medications and include, but are not limited to, the following:

Agents That May Affect Carbamazepine Plasma Levels

CYP 3A4 inhibitors inhibit carbamazepine metabolism and can thus increase plasma carbamazepine levels. Drugs that have been shown, or would be expected, to increase plasma carbamazepine levels include:

cimetidine, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clarithromycin, fluoxetine, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, ketoconazole, fluconazole, verapamil, valproate.*

CYP 3A4 inducers can increase the rate of carbamazepine metabolism. Drugs that have been shown, or that would be expected, to decrease plasma carbamazepine levels include:

cisplatin, doxorubicin HCl, felbamate, rifampin, phenobarbital, phenytoin, primidone, theophylline.

* Increased levels of the active 10,11-epoxide

† decreased levels of carbamazepine and increased levels of the 10,11-epoxide

Effect of Carbamazepine on Plasma Levels of Concomitant Agents

Increased levels: clomipramine HCl, phenytoin, primidone.

Carbamazepine induces hepatic CYP activity. Carbamazepine causes, or would be expected to cause, decreased levels of the following: acetaminophen, alprazolam, clonazepam, clozapine, dihydrofolate, doxycycline, ethosuximide, haloperidol, methsuximide, oral contraceptives, phenobarbital, phenytoin, theophylline, valproate, warfarin.

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75 and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Pregnancy: Teratogenic Effects: *Pregnancy Category C:* Carbamazepine has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg. In rat teratology studies, 2 of 135 offspring showed bifid ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; exophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

In humans, transplacental passage of carbamazepine is rapid (30-60 minutes), and the drug is accumulated in fetal tissues, with higher levels found in liver and kidney than in brain and lung.

There are no adequate and well-controlled studies in pregnant women. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Carbamazepine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, monotherapy is recommended for pregnant women.

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing

embryo or fetus.
Labor and Delivery: The effect of carbamazepine on human labor and delivery is unknown.
Nursing Mothers: Carbamazepine and its epoxide metabolite are transferred to breast milk. The ratio of the concentration in breast milk to that in maternal plasma is about 0.4 for carbamazepine and about 0.5 for the epoxide. The estimated doses given to the newborn during breast feeding are in the range of 2-5 mg daily for carbamazepine and 1-2 mg daily for the epoxide.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use: Substantial evidence of carbamazepine's effectiveness for use in the management of pediatric patients with epilepsy (see INDICATIONS AND USAGE for specific seizure types) is derived from clinical investigations performed in adults and from studies in several in vitro systems which support the conclusion that (1) the pathogenetic mechanisms underlying seizure propagation are essentially identical in adults and pediatric patients, and (2) the mechanism of action of carbamazepine in treating seizures is essentially identical in adults and pediatric patients.

Taken as a whole, this information supports a conclusion that the generally accepted therapeutic range of total carbamazepine in plasma (i.e., 4-12 mcg/mL) is the same in pediatric patients and adults.

The evidence assembled was primarily obtained from short-term use of carbamazepine. The safety of carbamazepine in pediatric patients has been systematically studied up to 6 months. Its longer-term data from clinical trials is available.
Geriatric Use: No systematic studies in geriatric patients have been conducted.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNINGS), the skin, and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:
Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.
Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.
Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.
Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.
Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.
Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence.
Albuminuria, glycosuria, elevated BUN and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving carbamazepine orally from 4-52 weeks at dosage levels of 50 to 400 mg/kg/day. Additionally, rats receiving carbamazepine in the diet for 2 years at dosage levels of 25, 75 and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.
Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, dystonias, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tremor, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Isolated cases of neuroleptic malignant syndrome have been reported with concomitant use of psychotropic drugs.
Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.
Eyes: Scattered punctate cortical lens opacities, as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.
Musculoskeletal System: Aching joints and muscles, and leg cramps.
Metabolism: Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with carbamazepine use (see PRECAUTIONS, Laboratory Tests). Decreased levels of plasma calcium have been reported.
Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol, and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with carbamazepine, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity
Lowest known lethal dose: adults, >40 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (8-year-old boy); small children, 5 g (3-year-old girl).

Oral LD_{50} in animals (mg/kg): mice, 1100-3750; rats, 3650-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms
The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>40 g) have been ingested.

Respiration: Irregular breathing, respiratory depression.
Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.
Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonus, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesis, bulbus, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.
Gastrointestinal Tract: Nausea, vomiting.
Kidneys and Bladder: Anuria or oliguria, urinary retention.
Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.
Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with carbamazepine may be aggravated or modified.

Treatment
The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, lavaging the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption: Activated charcoal, laxatives.
Measures to Accelerate Elimination: Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement translusion is indicated in severe poisoning in small pediatric patients.
Respiratory Depression: Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.
Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.
Convulsions: Diazepam or barbiturates.
Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week).
Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.
Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) ^{59}Fe-ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis and A_2 and F-hemoglobin, (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION (see table below)

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Tablets should be taken with meals.

Epilepsy: (See INDICATIONS AND USAGE.)
Adults and Children over 12 Years of Age
Initial: 200 mg b.i.d. Increase at weekly intervals by adding up to 200 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage should generally not exceed 1000 mg daily in children 12-15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. *Maintenance:* Adjust dosage to the minimum effective level, usually 800 to 1200 mg daily.
Children 6-12 Years of Age
Initial: 100 mg b.i.d. Increase at weekly intervals by adding 100 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage should generally not exceed 1000 mg daily. *Maintenance:* Adjust dosage to the minimum effective level, usually 400 to 800 mg daily.
Children Under 6 Years of Age
Initial: 10-20 mg/kg/day b.i.d. or t.i.d. Increase weekly to achieve optimal clinical response administered t.i.d. or q.i.d. *Maintenance:* Ordinarily, optimal clinical response is achieved at daily doses below 35 mg/kg. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the therapeutic range. No recommendation regarding the safety of carbamazepine for use at doses above 35 mg/kg/24 hours can be made.
Combination Therapy: Carbamazepine may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy: Teratogenic Effects: Pregnancy Category C).
Trigeminal Neuralgia: (See INDICATIONS AND USAGE.)
Initial: On the first day, 100 mg b.i.d. for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg/day using increments of 100 mg every 12 hours only as needed to achieve freedom from pain. Do not exceed 1200 mg daily. *Maintenance:* Control of pain can be maintained in most

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.
Eyes: Scattered punctate cortical lens opacities, as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.
Musculoskeletal System: Aching joints and muscles, and leg cramps.
~~**Metabolism:** Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of hyponatremia, with~~ decreased serum sodium (hyponatremia) and confusion, have been reported in association with carbamazepine use (see PRECAUTIONS, Laboratory Tests). Decreased levels of plasma calcium have been reported.
Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol, and triglycerides in patients taking anticonvulsants.
A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE
No evidence of abuse potential has been associated with carbamazepine, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE
Acute Toxicity
Lowest known lethal dose: adults, >40 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).
Oral LD_{50} in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.
Signs and Symptoms
The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>40 g) have been ingested.
Respiration: Irregular breathing, respiratory depression.
Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.
Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesis, hallucinations, psychomotor disturbances, dysmenia. Initial hyperreflexia, followed by hyporeflexia.
Gastrointestinal Tract: Nausea, vomiting.
Kidneys and Bladder: Anuria or oliguria, urinary retention.
Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.
Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with carbamazepine may be aggravated or modified.
Treatment
The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, lavaging the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.
Elimination of the Drug: Induction of vomiting.
Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.
Measures to Reduce Absorption: Activated charcoal, laxatives.
Measures to Accelerate Elimination: Forced diuresis.
Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small pediatric patients.
Respiratory Depression: Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.
Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.
Convulsions: Diazepam or barbiturates.
Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week).
Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.
Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.
Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) ^{59}Fe-kinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis and A_2 and F hemoglobin, (7) serum folic acid and B_{12} levels.
A fully developed aplastic anemia will require appropriate intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION (see table below)
Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Tablets should be taken with meals.
Epilepsy: (See INDICATIONS AND USAGE.)
Adults and Children over 12 Years of Age
Initial: 200 mg b.i.d. Increase at weekly intervals by adding up to 200 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage should generally not exceed 1000 mg daily in children 12-15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. *Maintenance:* Adjust dosage to the minimum effective level, usually 800 to 1200 mg daily.
Children 6-12 Years of Age
Initial: 100 mg b.i.d. Increase at weekly intervals by adding 100 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage should generally not exceed 1000 mg daily. *Maintenance:* Adjust dosage to the minimum effective level, usually 400 to 800 mg daily.
Children Under 6 Years of Age
Initial: 10-20 mg/kg/day b.i.d. or t.i.d. Increase weekly to achieve optimal clinical response administered t.i.d. or q.i.d. *Maintenance:* Ordinarily, optimal clinical response is achieved at daily doses below 35 mg/kg. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the therapeutic range. No recommendation regarding the safety of carbamazepine for use at doses above 35 mg/kg/24 hours can be made.
Combination Therapy: Carbamazepine may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy: Teratogenic Effects: Pregnancy Category C).
Trigeminal Neuralgia: (See INDICATIONS AND USAGE.)
Initial: On the first day, 100 mg b.i.d. for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg/day using increments of 100 mg every 12 hours only as needed to achieve freedom from pain. Do not exceed 1200 mg daily. *Maintenance:* Control of pain can be maintained in most patients with 400 to 800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level, or even to discontinue the drug.

HOW SUPPLIED
Carbamazepine Tablets USP, 200 mg
White, round, flat beveled-edge, one side scored and T-11 engraved on the other side.
Bottles of 100 ..... NDC 51672-4005-1
Do not store above 30°C (86°F).
Store in a dry place. Protect from moisture.
Dispense in a tight container, preferably glass as defined in the USP.

Dosage Information

Epilepsy			
Under 6 yr	10-20 mg/kg/day b.i.d. or t.i.d.	Increase weekly to achieve optimal clinical response, t.i.d. or q.i.d.	35 mg/kg/24 hr (see Dosage and Administration section above).
6-12 yr	100 mg b.i.d. (200 mg/day)	Add up to 100 mg/day at weekly intervals, t.i.d. or q.i.d	1000 mg/24 hrs
Over 12 yr	200 mg b.i.d. (400 mg/day)	Add up to 200 mg/day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hr (12-15 yr) 1200 mg/24 hr (> 15 yr) 1600 mg/24 hr (adults, in rare instances)
Trigeminal Neuralgia	100 mg b.i.d. (200 mg/day)	Add up to 200 mg/day in increments of 100 mg every 12 hours.	1200 mg/24 hours

Manufactured by: Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110
Distributed by: Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532

Revised: September 6, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074649

CHEMISTRY REVIEW(S)

ANDA 74-649

CHEMISTRY REVIEW: #3

NAME AND ADDRESS OF APPLICANT:

Taro Pharmaceuticals U.S.A., Inc.
Agent for: Taro Pharmaceutical Industries, Ltd.
Attention: Timothy A. Anderson
6 Skyline Drive
Hawthorne, NY 10532

PURPOSE OF AMENDMENT/SUPPLEMENT
Response to the agency deficiency letter dated November 22, 1995.

DATE(S) OF SUBMISSION(S)

Original application:	March 17, 1995
Amendment:	June 1, 1995
New correspondence	June 7, 1995
Amendment:	January 2, 1996
New correspondence:	January 17, 1996
New correspondence:	March 15, 1996
New correspondence:	April 19, 1996*
Labeling amendment:	August 20, 1996
Labeling amendment:	September 6, 1996

* It is relevant to note that apparently the correspondence dated January 2, was amended with Taro's letter dated January 17, and with the one dated March 15, 1996. On April 19, 1996, a telephone conference with Mr. M. Kohlbrenner, Associate Director, Research and Development was initiated by the reviewer, requesting clarification on the 3 letters listed above and how each interrelates with the OGD deficiency letter. Mr. Kohlbrenner explained that the amendment in response to our deficiency letter is the document dated January 2, 1996. All others are new correspondence.

PHARMACOLOGICAL CATEGORY
Anticonvulsant, trigeminal neuralgic associated pain

TRADE NAME	NONPROPRIETARY NAME	
N/A	Carbamazepine	
DOSAGE FORM	**POTENCY**	**RX OR OTC**
Tablet	200 mg	Rx
SAMPLES	**STERILIZATION**	
N/A	N/A	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074649

BIOEQUIVALENCE REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 74-649

DIV

Taro Pharmaceuticals U.S.A., Inc.
Attention: Michael Kohlbrenner
US Agent for: Taro Pharmaceuticals Industries, Ltd.
6 Skyline Drive
Hawthorne NY 10532

FEB 1 2 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Carbamazepine Tablets USP, 200 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of 1% sodium lauryl sulfate at 37°C using USP 23 apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

   Not less than (b)4 of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

(b)4 - Confidential Business

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-649 SPONSOR: Ivax Pharmaceutical
DRUG: Carbamazepine
DOSAGE FORM: Tablets
STRENGTH(s): 200 mg
TYPE OF STUDY: Single/~~Multiple~~ ~~Fasting/Fed~~
STUDY SITE: (b)4 - Confidential Business
STUDY SUMMARY:

The study is acceptable.

DISSOLUTION:

Dissolution testing is acceptable

PRIMARY REVIEWER: /S/ BRANCH: VII
INITIAL: /S/ DATE: 2/5/96

BRANCH CHIEF: BRANCH:
INITIAL: /S/ DATE: 2/5/96

DIRECTOR
DIVISION OF BIOEQUIVALENCE
for
INITIAL: /S/ DATE: 2/5/96.

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL: (b)4 - Confidential Business DATE:

FEB 2 1996

Carbamazepine
200 mg Tablets
ANDA #74-649
Reviewer: Moheb H. Makary
74649SD.395

Taro Pharmaceutical.
Haifa, Israel
Submission Date:
March 17, 1995
October 16, 1995

Review of a Bioequivalence Study and Dissolution Data

I. Objective:

Taro Pharmaceutical Industries Ltd. has submitted results of a comparative bioequivalence study and dissolution testing conducted on its test product, Carbamazepine Tablets, 200 mg, and Tegretol® Tablets, 200 mg, manufactured by Basel Pharmaceuticals as the listed reference product.

II. Introduction:

Carbamazepine is an anticonvulsant drug that is structurally similar to the tricyclic antidepressants. It is indicated for treatment of: 1) partial seizures with complex symptomalogy; 2) generalized tonic-clonic seizures; 3) some types of mixed seizures. Adults are initially treated with 200 mg bid, and the dose increased at weekly intervals by up to 200 mg/day given tid or qid until the desired response occurs. Maximum daily dosage is 1200 mg/day. In addition, carbamazepine is indicated for treatment of the pain associated with trigeminal neuralgia with an initial dosage of 100 mg bid. The innovator product is Tegretol Tablets 200 mg (Basel Pharmaceuticals; Ciba-Geigy Corporation); Tegretol Chewable Tablets 100 mg and Tegretol Oral Suspension 100 mg/mL.

Carbamazepine absorption is slow and variable due to poor water solubility. After a single 200-mg dose, plasma levels of 0.5-25 ug/mL (Cmax) may occur over 2-8 hours (average Tmax is about 4-6 hours). The oral availability is 70-100%. It is 70-80% bound to plasma proteins with a Vd about 1.4 L/kg. About 70% of a dose is excreted in the urine as metabolites, and about 2% appears unchanged. The remainder is excreted in the feces. One metabolite (carbamazepine-10,11-epoxide) is partially active. Carbamazepine has the property of autoinduction: its clearance increases with chronic dosing. After a single dose, the t1/2 ranges from 25-65 hours; at steady-state, steady-state, the t1/2 is about 15 hours (range of 12-17 hours). Therapeutic plasma levels average 4-12 ug/mL.

III. Protocol #9415014 For Single-Dose, Two-Way Crossover Bioavailability Study of Carbamazepine 200 mg Tablet Under Fasting Conditions:

Clinical site: (b)4 - Confidential

Analytical site: (b)4 - Confidential Business

Sponsor: Taro Pharmaceutical.
Haifa, Israel

Investigators: Clinical Investigator: (b)4 - Confidential
Bioanalytical: Business

Study design: Single-dose, randomized, 2-way crossover study, under fasting conditions

Subjects: Thirty (30) healthy adult male volunteers were selected to participate in this study. Twenty-four (24) subjects successfully completed the study in two groups.

Dose Date:	Period I	Period II
Subjects #1-21	10/15/94	11/5/94
Subjects #22	10/15/94	11/26/94
Subject #25-30	11/05/94	11/26/94

Subjects #23 and 24 were withdrawn from the study (disqualified) prior to receiving any study drug and the subject numbers were not reassigned.

Inclusion criteria: The subjects were between 18 and 51 years old. They were within 15% of their ideal weights (Table of "Desirable Weights of Adults", Metropolitan Life Insurance Company, 1983). Each subject received a complete physical examination and laboratory tests of hematopoietic, hepatic and renal functions. Only medically healthy subjects with clinically normal laboratory profiles and negative urine drug and alcohol prior to each phase were enrolled in the study.

Exclusions: Subjects with history or presence of:
-cardiovascular, pulmonary, hepatic, renal, hematological or significant gastrointestinal disease;
-hypersensitivity or idiosyncratic reaction to

carbamazepine or to any tricyclic antidepressant drugs; diabetes, or complications. were excluded from the study.

Restrictions: The consumption of alcohol beverages, xanthine and caffeine containing foods were prohibited for 48 hours, before dosing and throughout the period of sample collection. Subjects were instructed to take no over-the-counter medications (OTC) within 72 hours and no R_x within 14 days prior to start the study.

Dose and treatments: All subjects completed an overnight fast before any of the following drug treatments:

Test product: A. 2x200 mg Carbamazepine Tablets (Taro), lot #084-229, Exp. N/A, lot size (b)4 - tablets, content uniformity 103% (CV=0.65%), potency 102.5%.

Reference product: B. 2X200 mg Tegretol® Tablets (Basel), lot # 1T151824, Exp. 11/97, potency 98.9%.

Food and fluid intake: Single, oral 400 mg (2 Tablets) dose administered with 240 mL of water. Meals were provided at 4 and 10 hours after dosing. Fluids were allowed one hour before until 4 hours after dosing.

Blood samples: Blood samples were collected in heparinized tubes at: 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 15, 18, 21, 24, 48, 72, 96, 120, 144, and 168 hrs. Blood samples were centrifuged and the resultant plasma was separated. Plasma samples were immediately frozen at -10 °C until shipment.

Washout period: Three weeks

Assay methodology: Carbamazepine in plasma was measured using (b)4 - Confidential Business

Specificity:

Recovery:

(b)4 - Confidential Business

Sensitivity:

Linearty:

Precision:

(b)4 - Confidential Business

Stability:

Statistical Analysis:

ANOVA was performed at an alpha = 0.05 using the SAS-GLM. The 90% confidence intervals (2 one-sided t-test method) were calculated for LnAUC(0-t), LnAUCinf and LnCmax. A group term was included in the model.

IV. In Vivo Results:

Twenty-four subjects were initially entered in the study on October 15, 1994. Two subjects (#23 & 24) were disqualified prior to dosing and one subject (#11) voluntarily withdrew after dosing. Thus, 21 subjects completed period I. The intended number of subjects to complete the study was 24 subjects. Accordingly, the protocol was amended on October 18, 1994 to include 6 more subjects in the study. These 6 subjects were dosed on November 5, 1994 (period I) along with 17 subjects from the initial group (period II) of which two subjects (#14 & 8) were disqualified and two (#22 & 15) did not show up. On November 26, 1994, six subjects who started on November 5, 1994 and one subject (#22) who participated in the study on October 15, 1994 (agreed to show up on November 26, 1994) were dosed (period II). Thus, a total of 24 subjects completed the study. It should be noted that the sequence for subject #21 (chosen at random) was changed from B-A to A-B in order to balance the sequence in the two groups.

None of the adverse events experienced by the subjects during the study was judged to be serious. All adverse events are shown in Table I.

The plasma concentrations and pharmacokinetic parameters are summarized in Table II.

Table II

Mean Plasma Concentrations And Pharmacokinetic Parameters Following An Oral Dose of 400 mg (2x200 mg Tablets) Carbamazepine Under Fasting Conditions

(N=24)

Time (hr)	Taro Test product Lot #084-229 ng/mL (C.V.)	Basel Reference product Lot #1T151824 ng/mL (C.V.)
0	0.00	0.00
0.5	366 (40)	146 (94)
1	965 (35)	707 (50)
1.5	1446 (31)	1108 (42)
2	1794 (24)	1430 (36)
3	2389 (21)	1848 (30)
4	2681 (18)	2076 (31)
5	2869 (17)	2176 (30)
6	3022 (16)	2252 (25)
7	3083 (15)	2349 (22)
8	3065 (14)	2409 (21)
10	3175 (15)	2457 (20)
12	3144 (12)	2515 (18)
15	3199 (13)	2576 (16)
18	3122 (12)	2706 (16)
21	3064 (11)	2719 (16)
24	3163 (13)	2746 (15)
36	2735 (16)	2496 (15)
48	2362 (17)	2306 (17)
72	1583 (24)	1581 (25)
96	1044 (31)	1061 (33)
120	686 (38)	697 (40)
144	465 (45)	480 (46)
168	313 (55)	319 (60)

	Test	Reference	90% CI
AUC(0-t)(ng.hr/mL)	257147 (17)	238386 (19)	
AUCinf (ng.hr/mL)	277208 (21)	259349 (24)	
Cmax (ng/mL)	3416 (13)	2905 (17)	
Tmax (hr)	16	20	
Kel (1/hr)	0.0178	0.0179	
Half-life (hr)	40.2	40.2	
LnAUC(0-t)			103-114%
LnAUCinf			102-113%
LnCmax			110-123%

1. Taro's test product had an AUC(0-t) of 257147 ng.hr/mL and AUCinf of 277208 ng.hr/mL, which were 7.9% and 6.9% higher, respectively, than their reference product values. The differences were statistically significant. The 90% confidence intervals were within the acceptable range of 80-125% for log-transformed AUC(0-t) and AUCinf.

2. The Cmax of Taro's test product was 3416 ng/mL which was 17.6% higher than its reference product value. The difference was statistically significant . The 90% confidence interval of the test mean was within the acceptable range of 80-125% of the reference mean.

3. Carbamazepine plasma levels peaked at 15 and 24 hours for the test and reference products, respectively, following their administration under fasting conditions.

4. It should be noted that the statistical model used by the firm to assess the group effect was not the right model. The Division of Biometrics recommended using the following model:

Y = SEQ SUBJ(SEQ) PER TRT;

where the main effect PER has the values 1 (dosing on 10/15/94), 2 (dosing on 11/5/94),and 3 (dosing on 11/26/94).

Analysis of variance was performed by the reviewer using the above model resulted in the following 90% confidence intervals:

LnAUC(0-t)	103.9-113.2%
LnAUCinf	103.1-112.4%
LnCmax	113.0-123.9%

All confidence intervals remain within the acceptable 80-125% range.

V. Formulation:

Taro's formulation for Carbamazepine Tablets 200 mg is shown below:

Ingredient (amount per tablet)	200 mg Tablet
Carbamazepine, USP	200.00 mg
(b)4 - Confidential aqueous dispersion of ammonio methacrylate copolymer NF)	(b)4 - Confidential Business
Diethyl Phthalate NF	
Microcrystalline Cellulose, NF	
Starch NF	
Croscarmellose Sodium NF	
Magnesium Stearate NF	
Purified Water USP	

Total	**307.00 mg** **

* Evaporated during the [redacted](b)4 - [redacted]
** Does not include the purified water or the 70% aqueous component of [redacted](b)4 - Confidential Business[redacted]

VI. In Vitro Dissolution Testing:

Method:	USP 23 apparatus II (paddle) at 75 rpm
Medium:	900 mL of 1% sodium lauryl sulfate @ 37°C
Number of Tablets:	12
Test Products:	Taro's Carbamazepine 200 mg Tablets, lot #084-229
Reference Products:	Basel's Tegretol® 200 mg Tablets, lot #1T1151824
Specifications:	NLT [redacted](b)4 in 60 minutes

Dissolution testing results are shown in Table III.

VII. Comments:

1. The confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% under fasting conditions.

2. The in vitro dissolution testing for the test product, Carbamazepine Tablet, 200 mg is acceptable.

3. Carbamazepine, 200 mg tablet, manufactured by Taro Pharmaceutical Industries Ltd., exhibited higher mean values of dissolution than the reference product. This may correlate with higher plasma concentrations for the test product than the reference product.

4. The firm has submitted the plasma concentrations and pharmacokinetic parameters for Carbamazepine 10,11-epoxide. However, since this metabolite is not required for the approval of this submission, this data has not been reviewed.

VIII. Recommendations:

1. The single-dose bioequivalence study under fasting conditions conducted by Taro Pharmaceutical Industries LTD., on its Carbamazepine 200 mg Tablets, lot #084-229, comparing it to Tegretol® 200 mg Tablets manufactured by Basel Pharmaceuticals, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Taro's Carbamazepine, 200 mg Tablet is bioeqivalent to the reference product, Tegretol, 200 mg Tablet.

2. The dissolution testing conducted by Taro Pharmaceutical

Industries LTD., on its Carbamazepine 200 mg Tablet, lot #084-229 is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 1% sodium lauryl sulfate @ 37°C using USP 23 apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

> Not less than (b)4 of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

The firm should be informed of the above recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ Date: 11/2/95

Concur: /S/ Date: 2/2/96
for Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/11-1-95 wp 74649SD.395
cc: ANDA #74-552, original, HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-658 (Mhatre, Makary), Drug File, Division File.

Table III. In Vitro Dissolution Testing

Drug (Generic Name): Carbamazepine
Dose Strength: 200
ANDA No.: 74-649
Firm: Taro
Submission Date: March 17, 1995
File Name: 74649SD.395

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 75
No. Units Tested: 12
Medium: 900 mL of 1% sodium lauryl sulfate
Specifications: NLT (b)4 in 60 minutes
Reference Drug: Tegretol
Assay Methodology: (b)4

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 084-229 Strength(mg) 200			Reference Product Lot # 1T1151824 Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
15	64.8	(b)4 - Confidential Business	5.6	54.6	(b)4 - Confidential Business	2.8
30	82.7		4.5	73.2		2.4
45	92.0		4.5	83.6		2.0
60	97.0		3.2	89.6		1.8

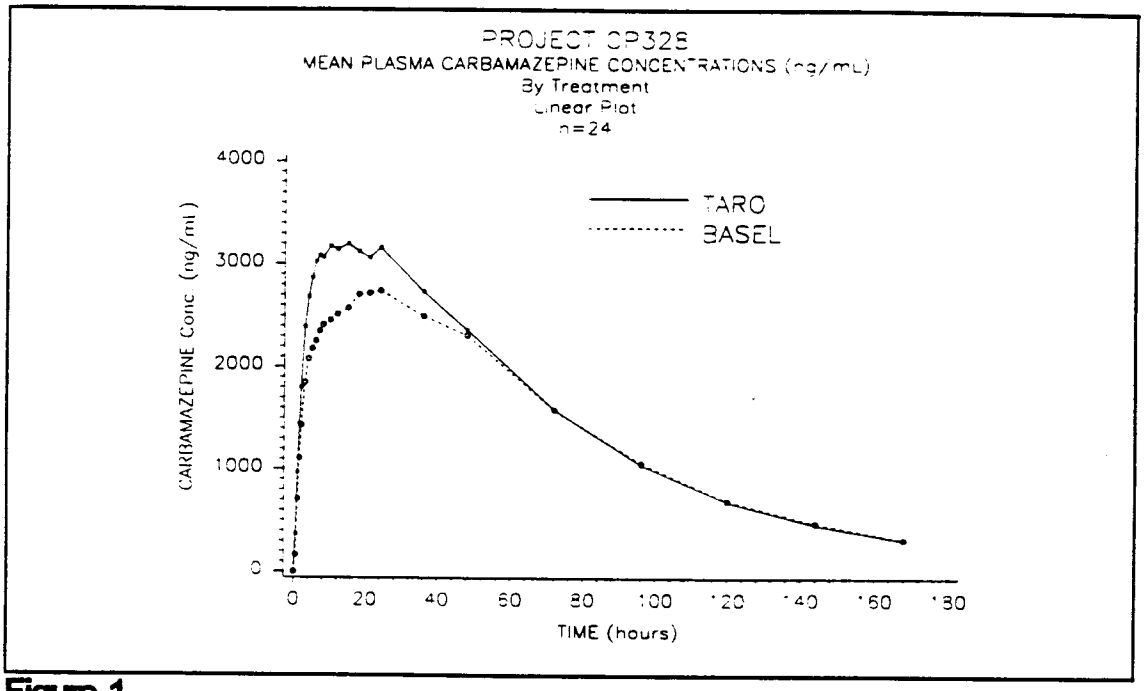


Figure 1

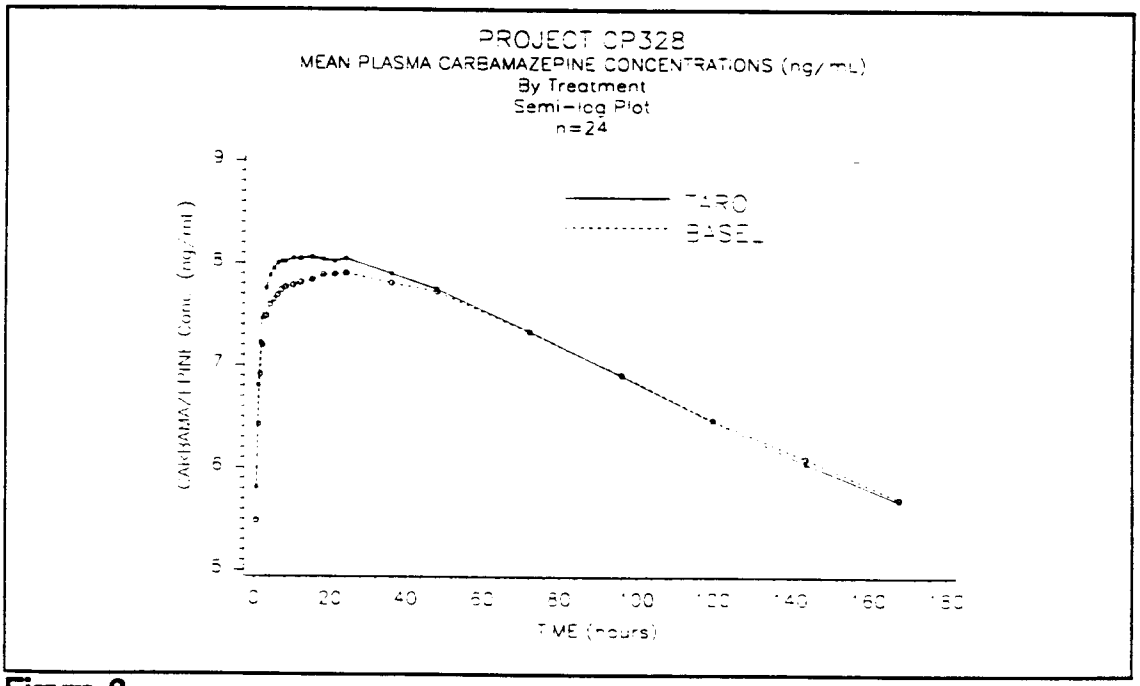


Figure 2

Table 1

CARBAMAZEPINE STUDY NO. 9415014C

Table 3: Summary of Adverse Events (Page 1 of 1)

Subject	Trt*	Adverse Event	ONSET		END		Ser[1]	Sev[2]	Act[3]	Rel[4]	Out[5]
			Date	Time	Date	Time					
01	na	Toothache	10/14/94	1835	11/03/94	1000	1	1	1	1	2
05	A	Headache	10/15/94	1030	10/15/94	1040	1	1	1	2	1
11	A	Nausea (bed rest, ginger ale given)	10/15/94	0940	10/15/94	1400	1	2	3	3	1
		Headache (cool compress given)	10/15/94	0945	10/15/94	1400	1	1	3	2	1
		Dizziness (bed rest, vital signs monitored)	10/15/94	1000	10/15/94	1400	1	1	3	1	1
20	B	Chlamydia (medical treatment, medication given)	10/24/94	2000	11/01/94	0730	1	2	3	1	1
29	A	Loose bowel movement	11/27/94	0900	11/27/94	0915	1	1	1	2	1

* Treatment: A-2 x 200 mg test tablets; B-2 x 200 mg Tegretol® tablets (Reference)
[1] Serious: 1-No; 2-Yes
[2] Severity: 1-Mild; 2-Moderate; 3-Severe
[3] Action Taken: 1-None; 2-Subject discontinued; 3-Other
[4] Relationship to Drug: 1-None; 2-Remote; 3-Possible; 4-Probable; 5-Definite
[5] Outcome: 1-Recovered; 2-AE continuing; 3-Subject lost to follow-up; 4-Other